"Genetic and Social Modifiers in Environmental Neuroepidemiology: The Role of Context in Chemical Exposure"

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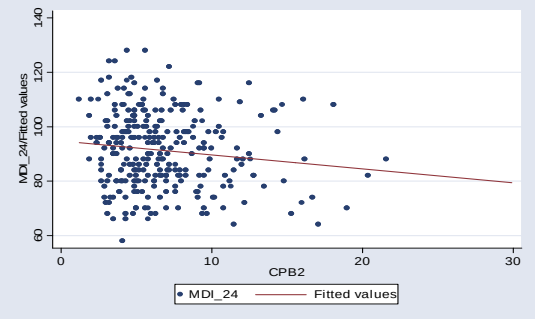
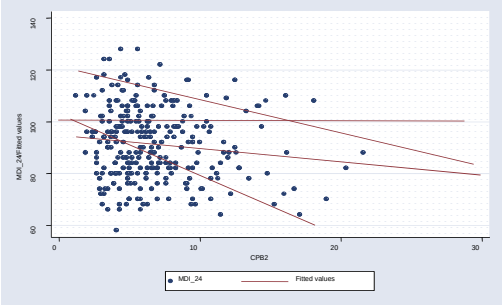


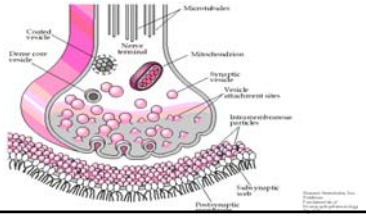


Biological Vulnerability

- Construction of the central nervous system (CNS) begins in utero,
- Continues throughout childhood and involves the production of 100 billion nerve cells and 1 trillion glial cells.
- Cell migrate, differentiate, and form synapses

Synapses

- Transmits signals between neurons
  - Environmental stimuli will cause neurons to fire
  - Neuronal/synaptic firing is a signaling process to mold the synaptic architecture of the brain



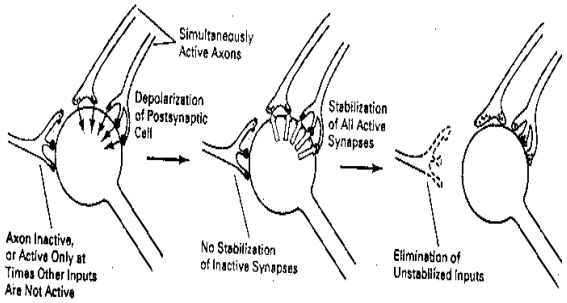
How does the Brain Build this Network?

- Some of it is stochastic
  - Synapses are made by the billions, and in some respects randomly, between neurons.
  - We make a net gain in synapses from fetal life till about age 2 years
  - Then the number of synapses in our brain starts to decrease
    - Why?

Synaptic Networks

- Environmental Stimuli cause nerves to fire:
- When they fire neurotransmitters are released into synaptic junctions
  - This releases growth factors- signals that this is an important neuronal connection (i.e. it gets used)
- In other words there is a “natural selection” process
  - Functional synapses release growth factors
  - Nonfunctional synapses do not release the growth factors

Hebb Synapses



So how do Environmental Chemicals affect Development?

- At “low” doses (blood lead around 5-10 ug/dL)
  - Lead will interact with Protein Kinase C
    - Stimulate neurotransmitter release
    - Neurons fire in the absence of an appropriate environmental stimuli
  - Lead mimics calcium
    - Calcium is critical to nerve signal transmission
    - Calcium enters neurons during depolarization
    - Lead blocks calcium channels

Lead and the Brain

- Net effect
  - Lead stimulates nerves to fire in a more stochastic fashion
  - Lead also inhibits neurotransmission (both appropriate neurotransmission and inappropriate neurotransmission)
- Changes the underlying synaptic architecture, making it less efficient

Plasticity

- The brain’s capacity to diminish the effects of toxic insults through structural/functional changes
  - This occurs through the same processes as synaptic selection
  - In other words plasticity allows for new connections to be made which improve function following an insult
- Maladaptive vs adaptive plasticity

Neurodevelopment and Social Environment

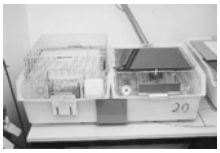
- **Chronic Stress known to impair memory and learning capacity**

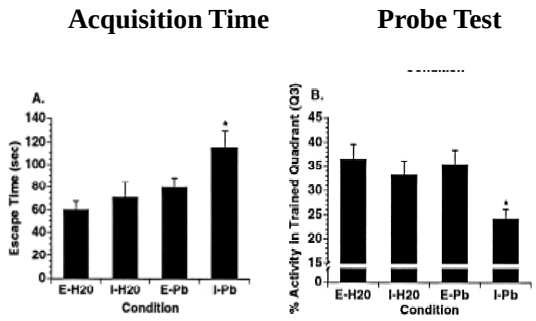
Non-chemical Toxicants- Psychological Stress

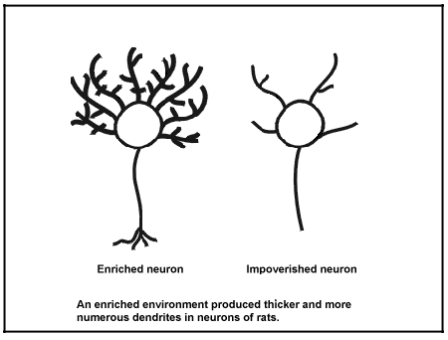
- Psychological stress - activates HPA axis Increases cortisol
- Hippocampus - highest density of glucocorticoid receptors
  - modulate neuro and synaptogenesis
  - acutely, stress enhances memory formation,
  - chronic stress appears to inhibit it

Social Environment and Pb

- Guilarte et al
- Lead poisoned animals during lactation
- Randomized to 2 groups
  - Animals raised in social isolation
  - Animals raised in groups with social stimulation
    - Tested on memory in Water maze







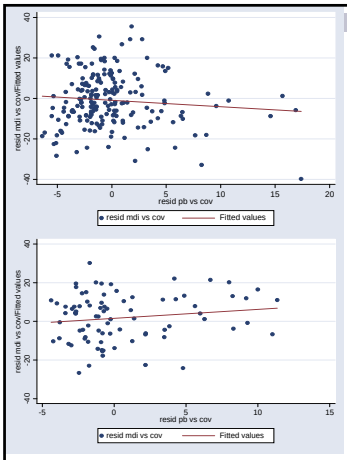
Can Reducing Stress be a Treatment?

- Mexico City
- Coopersmith self-esteem administered to mothers when child 24 months of age
- Cross-sectional analysis
- Covariates
  - Blood Pb, mom's IQ, mom's education, child's sex,

Main Effect of Maternal Self-Esteem

mdi24	Coef.	P>|t|	[95% CI]	
Blood Pb	-.11	0.569	-.50	.276
autoes	***.46***	***0.006***	***.12***	***.78***

Adjusted for Maternal IQ, education, Infant Sex,

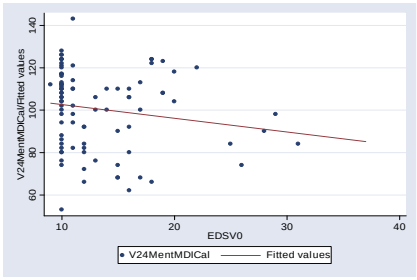


Blood Pb and MDI

Self esteem Quartile 1,2,3

Self esteem Quartile 4

Maternal Depression scale at delivery vs 24 month MDI



Another Pilot Study: Maternal Child Lung Study

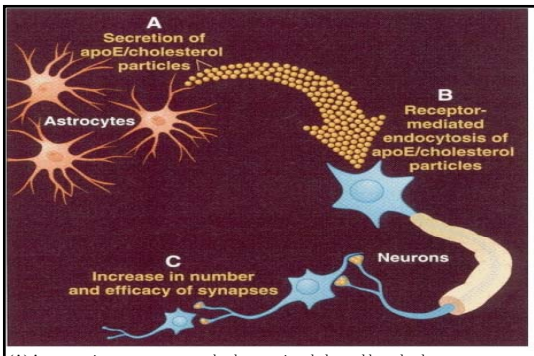
- Pregnancy cohort recruited from 1986-1992
- Study of in utero/environmental tobacco smoke exposure and respiratory outcomes
- Women enrolled before 20th EGA week
- Children followed after birth
- Measured ETV (violence) and WCST as pilot

Effect of Cotinine in Predicting Errors on WCST: Stratified by Median Violence Exposure

	Cotinine Beta (Low violence)	Cotinine Beta (High violence)
% Errors	2.9 (p=0.6)	9.8 (p=0.07)
# Perseverative Responses	1.7 (p=0.7)	11.1 (p=0.007)
%Perseverative Responses	2.0(p=0.7)	10.7 (p=0.007)
# Perseverative Errors	0.8 (p=0.9)	10.7 (p=0.01)
% Perseverative Errors	1.4 (p=0.8)	9.9 (p=0.02)

How Does Genetics play into this?

- Genetics regulates synapse formation
  - Pruning
  - Maintenance
    - Growth factors
    - Protection from oxidative xenobiotics
    - Nutrition



(A) Astrocytes increase synapse number by secreting cholesterol bound to large lipoprotein particles containing apolipoprotein E (apoE).
(B) These particles are internalized by neurons, leading to increased cholesterol within neuronal membranes. It is possible that apoE also activates yet to-be-identified signaling pathways within the neurons.
(C) These changes stimulate an increase in the number and efficacy of synapses.
From: Barres: Science, Volume 294(5545).November 9, 2001.1296-1297

APOE and Neurodegeneration

- E4 allele associated with 2-5 fold increased risk of AD if heterozygote
  - 5-17 fold increased risk if homozygote

APOE and Neurodevelopment

- Study of lead exposure and infant development in Mexico.
- Infants enrolled at birth, cord lead levels measured, Mothers receive calcium supplements in RCT.
- Bayley Infant Development scales performed at 24 months of age.

APOE and Neurodevelopment

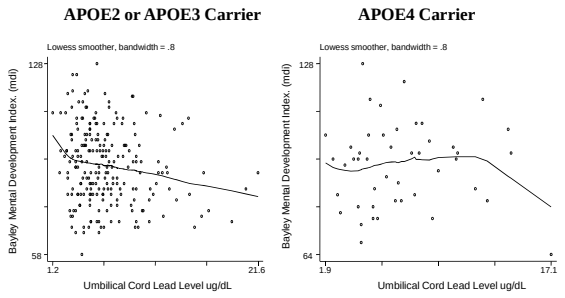
Multivariate Analysis	Beta
#APOE4	4.3(95% CI: 0.03 – 8.5)

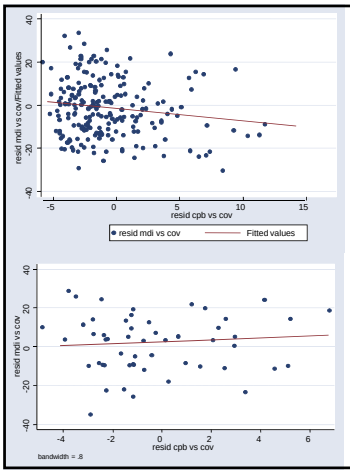
Study Group- subjects E4/E3. E4/E4

Referent group- subjects E3/E3, E3/E2, E2/E2

OR adjusted for the maternal IQ, Sex, gestational age, dietary calcium, umbilical cord blood lead level and Maternal years of Education.

Figure 1: Smoothed Plots of MDI Score vs Umbilical Cord Lead Levels





C2 Genotype as Modifier of Cord Pb Effect

Transferrin C2 Wildtype

Transferrin C2 Carrier

Metal Mixtures

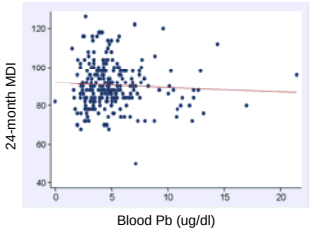
- Just as exposure does not occur uniformly against a given social context.
- Exposure to Neurotoxicants is mixed.
  - Pb
  - Mn
- Both have evidence of neurotoxicity.

Mexico City

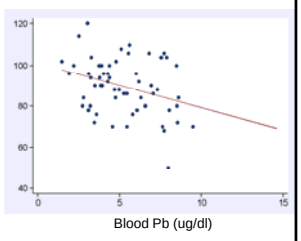
- Blood Mn measured on 300 infants at 1 year of age from archived samples.
- Blood Pb measured at 12, 18 and 24 months
- Bayley MDI at 12, 18 and 24 months.

Blood Pb and 24-month MDI Association Varies by Blood Mn Level

Lowest 4 Quintiles of Blood Mn



Highest Quintile of Blood Mn



Interaction beta: -1.5, p=0.04 (N=290)

Manganese-Lead Interaction

Highest Quintile of Blood Mn x Blood Pb

	Adjusted beta*	p
12-month MDI	-0.66	0.28
18-month MDI	-1.4	0.02
24-month MDI	-1.5	0.04
Repeated Measures	-0.9	0.04

*Adjusted for 12-month blood Pb level, infant sex, maternal IQ, maternal education

Mexico Birth cohort

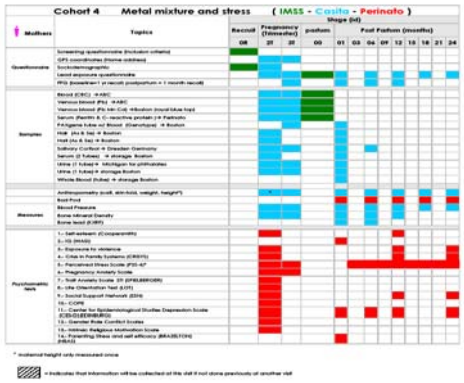
- The work just reviewed led to the establishment of a new birth cohort in Mexico City.
- 1) R01 ES014930 Metal Mixtures and Neurodevelopment
- 2) R01 ES013744 Stress, Lead, Iron Deficiency and Neurodevelopment.

Mexico City Birth Cohort

- Designed to study
  - Prenatal vs post-natal contributions to development
  - Genetic susceptibility
  - Metal mixtures
  - Social modifiers of toxicity

Mexico City Cohort

- Long term goals
  - Identify factors that increase/decrease metal toxicity
  - Understand the biology of metal neurotoxicity
  - Prevent toxicity
  - Treat toxicity after it has occurred



Tar Creek Superfund Site

The *MATCH* Study

(Metals **A**ssessment **T**argeting **C**ommunity **H**ealth**)**

"Ga-Du-Gi"- Working Together

Thanks

Element
Adrienne Ettinger
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Rosalind Wright
Howard Hu
Lourdes Schnaas
Adriana Mercado

Tar Creek
Mary Happy
Mark Osborn
Rebecca Jim
Earl Hatley

Criminal Behavior as a Late Outcome of Early Exposure to Environmental Lead

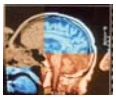
Cincinnati Lead Study

Kim N. Dietrich, Ph.D.

Environmental Factors in Criminal Disposition

- Parental dysfunction
- Community violence
- Poverty
- Media
- Lead
- Nutrition
- Alcohol
- Illicit Drugs

Biological Factors in Criminal Disposition



- Functional Anatomical Characteristics of Brain
- Neurotransmitter Metabolism
- Autonomic Function
- Traumatic Brain Injury (Frontal Lobes)
- Genetic endowment (Functional Polymorphisms)

Criminal Behavior as an Outcome of Childhood Lead Poisoning

Lead Exposure and Juvenile Delinquency: Earlier Observations

1943: Byers and Lord reported a high prevalence of behavior problems among survivors of lead encephalopathy. "…violent aggressive behavioral difficulties such as attacking teachers with knives and scissors."

Byers & Lord, *Am J Dis Child. 1943*

Dr. Randolph Byers

Bone Lead Levels and Percentage of Children Scoring in the Clinical Range for Aggression, Delinquency, and Attention on the Achenbach Child Behavior Check List

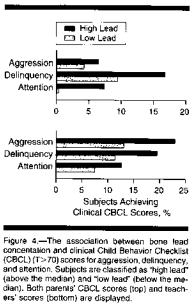


Figure 4.—The association between bone lead concentration and clinical Child Behavior Checklist (CBCL) (T>70) scores for aggression, delinquency, and attention. Subjects are classified as "high lead" (above the median) and "low lead" (below the median). Both parents' CBCL scores (top) and teachers' scores (bottom) are displayed.

Needleman, et al., JAMA, 1996.

Bone Lead Levels (ppm) in Adjudicated Delinquents: A Case Control Study*

	Cases		Controls		*P value*
	n	Mean (SD)	*n*	Mean (SD)	
All Subjects	195	11.0 (32.7)	150	1.5 (32.1)	0.007
African-American	158	9.0 (33.6)	51	-1.4 (31.9)	0.05
White	36	20.0 (27.5)	95	3.5 (32.6)	0.008

*Needleman, et al. 2002, Neurotoxicol Teratol.

Other Observations: Ecological Studies

- Stretesky and Lynch (2001) reported positive correlations between homicide rates and air lead contamination levels for 3111 counties in the US. Even after adjustment for 15 confounding variables, a four-fold increase in homicides in the counties with the highest air lead concentrations compared to counties with the lowest air lead concentrations was found.

  Stetesky & Lynch, *Arch Pediatr Adolesc Med., 2001*

- Nevin (2000) reported a statistically significant relationship between trends in sales of leaded gasoline and violent crime after adjustment for such variables as unemployment rates and percent of population in the age range where there is a higher risk for criminal behavior.

  Nevin, *Environ Res.,* 2000

Limitations of Earlier Studies

- These studies suggest that exposure to environmental lead during childhood is associated with the development of behavioral problems, delinquency and criminality.
- Questions remain, however, because the majority of these studies were cross-sectional, relied on indirect measures of lead exposure or did not follow the children into adulthood to examine the relationship of lead exposure with persistent criminality.

The Cincinnati Lead Study of Juvenile Delinquency and Adult Criminality

Cincinnati Lead Study catchment area

The Cincinnati Lead Study

- A prospective, longitudinal study initiated in 1979 that is examining the early and late effects of childhood lead exposure on growth and development with a particular emphasis on neurobehavioral outcomes.
- The Cincinnati Lead Study has collected data on exposure (blood lead concentrations), neurobehavior, child health, and sociodemographic variables on a quarterly to yearly basis since its inception.

Blood Lead Concentrations in the Cincinnati Lead Study

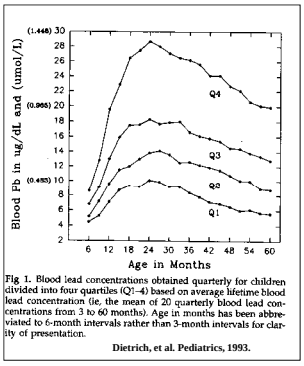
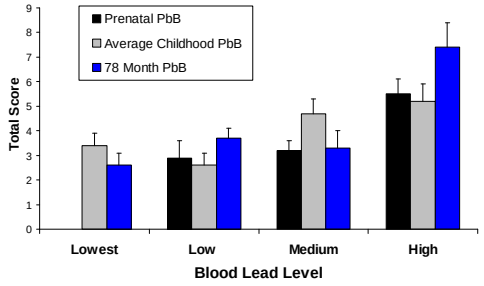


Fig. 1. Blood lead concentrations obtained quarterly for children divided into four quartiles (Q1–4) based on average lifetime blood lead concentration (ie, the mean of 20 quarterly blood lead concentrations from 3 to 60 months). Age in months has been abbreviated to 6-month intervals rather than 3-month intervals for clarity of presentation.

Dietrich, et al. Pediatrics, 1993.

Association of Blood Lead Levels and Self-Reported Delinquency in 16 Year-Old Adolescents in the Cincinnati Lead Study



Dietrich, et al. 2001, Neurotoxicol Teratol.

Cincinnati Lead Study Cohort as Adults (N = 250)

Characteristic	No. (%) / Mean (SD)
Subject Characteristics	
Male	125 (50.0%)
African-American	225 (90.0%)
Age at study date (years)	**22.5 (1.5)**
Marijuana use	29 (11.6%)
Blood lead (μg/dL)*	
Prenatal blood lead**	8.3 (3.8)
Average childhood blood lead	13.4 (6.1)
6-year blood lead	8.3 (4.8)

Cincinnati Lead Study Cohort as Adults (N = 250)

Maternal Characteristics	No. (%) / Mean (SD)
Age at delivery (years)	22.5 (4.2)
Maternal IQ (points)	75.3 (9.3)
High School graduate	132 (52.8%)
HOME Inventory at age 3 (points)	32.3 (6.6)
Socioeconomic status (Hollingshead score)	18.0 (4.8)
History of arrest (yes)	111 (44.4%)
Marital Status	
Married	39 (15.6%)
Single	155 (62.0%)
Other	56 (22.4%)
Smoked during pregnancy	129 (51.6%)
Number of children in home	3.0 (1.4)
Public assistance	190 (76%)

Table: Relationship of Prenatal, Early Childhood Average and Six-Year Blood Lead Concentrations with Arrests Rates in Young Adults (N = 250)

		Adjusted Estimates*	
Blood Lead Variable	Median (5^{th}-95^{th} percentile) μg/dL§	Attributable Risk (95%CI) per year	Rate ratio for 5 μg/dL increase in blood lead (95% CI)
Prenatal	7.8 (2.9-16.0)	0.48 (0.29-0.79)	1.40 (1.07-1.85)
Early Childhood Average	12.3 (6.0-26.3)	0.13 (0.03-0.33)	1.07 (0.88-1.29)
Six-Year	6.8 (3.4-18.3)	0.39 (0.21-0.68)	1.27 (1.03-1.57)

*Adjusted for maternal IQ, sex, socioeconomic status (SES) using the Hollingshead Score, and primary caregiver education level.

§Convert to umol/L ([ug/dL] x 0.04826)

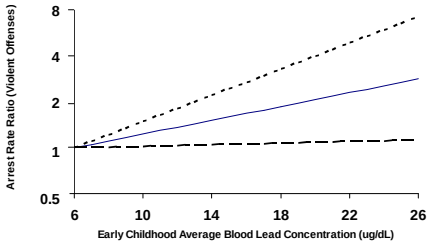
Table: Relationship of Prenatal, Early Childhood Average and Six-Year Blood Lead Concentrations with Violent Arrests Rates in Young Adults (N = 250)

		Adjusted Estimates*	
Blood Lead Variable	Median (5^{th}-95^{th} percentile) μg/dL§	Attributable Risk (95% CI) per year	Rate ratio for 5 μg/dL increase in blood lead (95% CI)
Prenatal	7.8 (2.9-16.0)	.055 (.026-.118)	1.34 (0.88-2.03)
Early Childhood Average	12.3 (6.0-26.3)	.077 (.039-.156)	1.30 (1.03-1.64)
Six-Year	6.8 (3.4-18.3)	.087 (.049-.152)	1.48 (1.15-1.89)

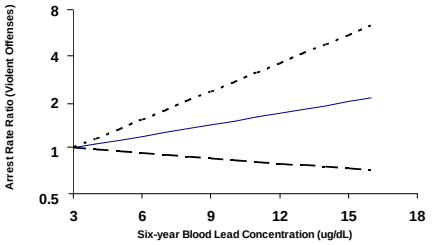
*Adjusted for maternal IQ, sex, socioeconomic status (SES) using the Hollingshead Score, and primary caregiver education level.

§Convert to umol/L ([ug/dL] x 0.04826)

Blood Lead Concentrations and Arrests for Violent Offenses in the Cincinnati Lead Study



Blood Lead Concentrations and Arrests for Violent Offenses in the Cincinnati Lead Study



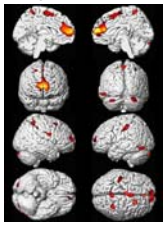
Mechanisms: How Does Lead Increase Antisocial Behavior?

- Direct route: Lead affects brain systems that regulate social-emotional functioning, including neurotransmitter metabolism and function, and neural growth, survival and differentiation in critical areas such as prefrontal cortex. Gene-environment interactions may also play a role.
- Indirect route: Early lead exposure is associated with higher rates of school failure and reading disabilities. Students who do poorly in school are more likely to engage in delinquent and criminal activities.

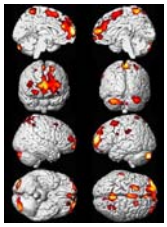
Biological Underpinnings: Imaging Studies of the Cincinnati Lead Study Cohort

Mechanism: Lead Associated Gray Matter Loss in Brain*

Average Childhood PbB



Six-Year PbB



*The effects of lead on gray matter loss were most severe in the frontal regions of the brain which are involved in attention, executive functions, and regulation of social behaviors.

Summary

- Data from previous cross-sectional and ecological studies suggest an association between exposure to lead and antisocial behaviors including delinquency and adult criminality.
- Data from the Cincinnati Lead Study indicate an association between prenatal and early postnatal exposure to lead and delinquent and criminal behaviors.
- Neuroimaging studies of the Cincinnati Lead Study cohort indicate lead-associated losses in gray matter of the cerebral cortex in areas of the brain that regulate attention, executive functions, judgment and social behaviors.

Questions and Discussion